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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,677	02/21/2002	Alan Korman	NEX85/PCT-US	9102

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EXAMINER	
CALAMITA, HEATHER	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,677	KORMAN ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-15, drawn to a nucleic acid ligand and the method for isolation of nucleic acid ligands to CD40 Ligand .

Group II, claim(s) 16-18, drawn to methods of treatment using a nucleic acid ligand to CD40 Ligand.

Group III, claim(s) 19-21, drawn to a pharmaceutical composition.

The inventions listed as Groups I, II and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions are linked by the technical feature of the modulation of CD40 Ligand. However, this feature is not special because it does not constitute an advance over the prior art. Armitage et al. (USPN 6087329) teach the modulation of CD40 Ligand.

The special technical feature of invention groups II, methods of treatment using a nucleic acid ligand to CD40 Ligand, is the use of a nucleic acid to modulate CD40 ligand to treat disease arising form T-cell activation and is not present in invention groups I and III. The special technical feature of invention groups I, a method for isolation of nucleic acid ligands to CD40 Ligand, is the use of both a hybridization detection step and an amplification step that is not present in invention groups II and III.

Sequence Election Requirement Applicable to All Groups

2. In addition, each Group detailed above reads on patentably distinct Groups drawn to multiple SEQ ID Numbers. The sequences are patentably distinct because they are unrelated

sequences, and a further restriction is applied to each Group. Furthermore, the sequence searching in multiple expansive databases has put undue burden on the examiner and office resources. For an elected Group drawn to amino acid sequences, the Applicants must further elect a single amino acid sequence. For an elected Group drawn to nucleotide sequences, the Applicants are permitted to elect a **single nucleic acid sequence** (See MPEP 803.04).

MPEP 803.04 states:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided sua sponte to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996).
>
> It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, **up to** ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

During a telephone conversation with Rosemary Kellogg on September 13, 2004, a provisional election was made without traverse to prosecute the invention of Group II, claim16-18. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-15 and 19-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of

inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112 - Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the treatment of disease by *in vivo* host cell modulation of CD40 ligand using the aforementioned nucleic acid ligands. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to administering nucleic acid ligands for treatment of diseases correlated with CD40 ligand expression which comprise isolated nucleic acid ligands and host cells, which includes cells *in vivo*, that are used for *in vivo* protein expression modulation methods for treatment. The

invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method for treating various CD40 ligand associated diseases which use the administration of aptamers in humans. No specific chemical compounds which function to modulate the expression of CD40 ligand have been identified in the specification. No specific type of CD40 ligand associated disease is recited and thus the claims encompass any variant of the disease, whether involving overexpression of CD40 ligand, underexpression of CD40 ligand as well as downstream effects of CD40 ligand in which an altered protein may otherwise cause disease but be expressed at normal levels.

Quantity of Experimenation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the candidate CD40 ligand binding nucleic acid mixture to demonstrate proof of principle. That is, prior to any therapeutic intervention, it would be necessary to isolate a candidate mixture of CD40 ligand binding nucleic acid mixture, ascertain an appropriate amount of the aptamer mixture to administer in order to have some effect, determine which modifications to make to the aptamer to prevent degradation by nucleases, then show the presence of the aptamers would have some therapeutic effect on cells, a series of showings not present in the specification. Following such experimentation, animal models would need to be characterized, an inventive, unpredictable and difficult undertaking in itself, and efficacy would need to be demonstrated in such animal models. In Nature Reviews Genetics (1:116-125) Stockwell states, regarding aptamers, "It is, however, difficult to screen exogenous ligands in whole animals, such as mice, because of the difficulty and expense of testing numerous ligands in animals (see page 123 column 2 paragraph 2)." This would require years of inventive effort, with each of the many

intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art teaches that treatment of disease with aptamers is one of the most unpredictable areas of human endeavor for which patents are sought.

Stull and Szoka, in 1995 (Pharmaceutical Research 12:465-483) state regarding the use of aptamers in *in vivo* therapy "application of these compounds (aptamers) *in vivo* requires many problems be solved (see page 476, column 2, paragraph 1)." Stull and Szoka further describe the difficulties with persistence of effect, access to the target cells and efficient cytoplasmic delivery of the drug (see page 476, column 2, paragraph 1). They further note, "none of the modalities proposed to date can eliminate the disease/target. Thus suppression of disease will require the continued presence of the agent...(see pages 476, column 2 last paragraph and 477 column 1)."

The prior art teaches that methods of using aptamers for treatment of disease are currently unpredictable when using injection mediated delivery approaches. Stull and Szoka relate in spite of the numerous delivery reagents that have been developed (i.e. modification of the ionic backbone, attachment of cholesterol and attachment of targeting ligand such as biotin to the nucleic acid) problems with delivery still exist, with the aptamers frequently taken up in endosomes (see page 477 column 1 last paragraph and column 2). Aptamers continue to have problems with poor stability and persisting effects, Andreola et al., in 2000 (Eur. J. Biochem 267:5032-5040) describe the continued problems with stability, nuclease resistance and half-life *in vivo* (see page 5032 column 2 last paragraph). Further Tuddenham (Nature 419:23-24) in a 2002 review points out that *in vivo* studies are now under way in animals (see page 24, column 1).

The prior art also supports the unpredictable nature of the art. It is unpredictable which formulations, compounds and delivery modes will function in an *in vivo* setting. This unpredictability is

evidenced by Stull and Szoka who state that "To date, only a few instances of oligonucleotide aptamers displaying biological effects have been reported (see page 466 column1 paragraph 1)." Thus, the prior art not only fails to support the efficacy of the invention, but in fact, supports the unpredictability of this area of technology.

Working Examples

The specification has no working examples, whatsoever, of treatments which modulate the expression of CD40 ligand by administering a nucleic acid ligand to CD40 ligand.

Guidance in the Specification.

The specification, while mentioning gene therapy, provides absolutely no guidance whatsoever on modes and means of performing gene therapy. No specific teachings regarding the use of the particular nucleic acid ligand constructs with any success is presented. No teachings are provided that the nucleic acid ligand constructs claimed are able to satisfactory modulate the expression of CD40 ligand over a sufficiently long term to be efficient as a therapeutic agent and no teachings are provided as to the amount of nucleic acid ligand that would have to be provided or the lengths of time over which such nucleic acid ligands would have to be provided to effectively treat disease correlated with CD40 ligand expression. It would essentially be a trial and error process to use the nucleic acid ligand molecules encompassed by the claims, and to administer these at a satisfactorily high level for a sufficient period of time within a human being or other animal model. It is further not predictable that these nucleic acid ligands to CD40 ligand would be effective to achieve any therapeutic benefit in modulating CD40 ligand expression on host cells.

Level of Skill in the Art

The level of skill in the art is deemed to be high with regard to the practitioners but low relative to the ability to treat disease by administering aptamers, since as of the filing date of this application,

treatment of disease by *in vivo* administration of aptamers had never been attempted (see Tuddenham, page 24, column 1 where the only *in vivo* studies underway were animal studies).

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high (see Stockwell, Stull and Szoka, Andreola et al. and Tuddenham), the specification provides one with no written description or guidance that leads one to a reliable method of treatment. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in gene therapy required to actually use the nucleic acid ligand sequences recited in a treatment as broadly claimed (i.e. encompassing a method for the treatment of a disease resulting from T cell activation by administering a nucleic acid ligand to CD40 ligand). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is an inescapable conclusion that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Summary

3. No claims were allowed.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita, Ph.D. whose telephone number is 571.272.2876 and whose e-mail

address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday thru Thursday 7:00 A.M. - 5:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571.272.0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

hgc

JEFFREY FREDMAN
PRIMARY EXAMINER
9/29/04